JOC*Note*

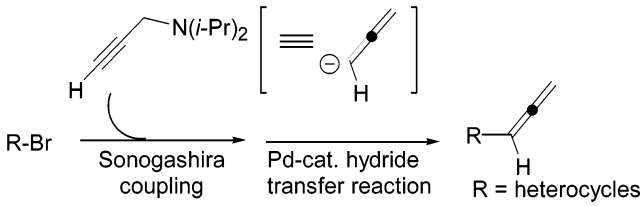
Synthesis of Heterocyclic Allenes via Palladium-Catalyzed Hydride-Transfer Reaction of Propargylic Amines

Hiroyuki Nakamura,* Shinya Onagi, and Takaya Kamakura

Department of Chemistry, Faculty of Science, Gakushuin University, Mejiro, Toshima-ku, Tokyo 171-8588, Japan

hiroyuki.nakamura@gakushuin.ac.jp

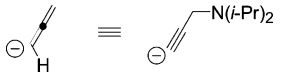
Received November 17, 2004



Propargylic diisopropylamines containing heterocycles, which were prepared readily from heterocyclic bromides and propargyldiisopropylamine by the Sonogashira coupling reaction, underwent the allene transformation reaction in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst (2.5 mol %) and 1,2-bis[bis(pentafluorophenyl)phosphino]ethane (10 mol %) at 100 °C in $CHCl_3$, giving the corresponding heterocyclic allenes in good to high yields via the palladium-catalyzed hydride-transfer reaction.

Allenes are now very important building blocks for organic synthesis.[1−5] In general, allenes can be prepared from propargyl alcohol derivatives by S_N2'-type displacement with organocopper species.[6] Other preparation methods include the homologation of 1-alkynes,[7] the stereoselective reduction of alkynes,[8] asymmetric allylations,[9,10] β-eliminations by Horner−Emmons−Wadsworth[11] or sulfinyl radical[12] reactions, and palladium-catalyzed hydrogenolysis[13] or coupling reactions of allenylstannanes,[14] allenylindiums,[15] and allenylzincs[16] have been recently reported. However, there are few examples of the synthesis of allenes containing heterocycles[15a] due to unexpected interactions between the substrates and reagents (or catalysts), which would interrupt the reaction progress. We recently found that propargylic amines underwent the hydride-transfer reaction in the presence of a palladium catalyst to afford allenes.[17] In this transformation, propargylic amines can be handled as an allenyl anion equivalent and introduced into various electrophiles to be transformed into allenes (Scheme 1). In this paper, we report the synthesis of heterocyclic allenes from the corresponding propargylic amines via the Sonogashira coupling followed by the palladium-catalyzed hydride-transfer reaction.

SCHEME 1. Concept of an Allenyl Anion Equivalent



The heterocyclic allene precursors were synthesized using the Sonogashira coupling reaction of *N*,*N*-diisopropylprop-2-ynylamine with various heterocyclic bromides (R-Br).[18] The results are shown in Table 1. The reactions were carried out in the presence of $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %) and Et_3N (150 mol %) in CH_3CN at 60 °C. The propargylic diisopropylamines **1a**−**f** were obtained from the corresponding bromides in 67−99% yields (entries 1−6). The reaction of 3-bromo-benzo[*b*]thiophene with *N*,*N*-diisopropylprop-2-ynylamine also proceeded under the same conditions to give the corresponding propargylic diisopropylamine **1g** in 51% yield (entry 7). Although 5-bromoindole did not undergo the Sonogashira coupling reaction, the reaction of *N*-Boc-5-bromoindole

(1) (a) *The Chemistry of Allenes*; Landor, S. R. Ed.; Academic Press: London, 1982. (b) Hoffmann-Roder, A.; Krause, N. *Angew. Chem., Int. Ed*. **2002**, *41*, 2933. (c) *Modern Allene Chemistry*; Krause, N., Hashmi, S., Eds.; Wiley-VCH: Weinheim, 2004.

(2) For transition-metal-catalyzed reactions, see: (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc*. **1994**, *116*, 6019. (b) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc*. **1995**, *117*, 5156. (c) Franzén, J.; Löfstedt, J.; Dorange, I.; Bäckvall, J.-E. *J. Am. Chem. Soc*. **2002**, *124*, 11246. (d) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc*. **1995**, *117*, 1843. (e) Ahmed, M.; Amauld, T.; M. Barrett, A. G.; Braddock, D. C.; Flack, K.; Procopiou, P. A. *Org. Lett*. **2000**, *2*, 551. (f) Lu, C.; Lu, X. *Org. Lett*. **2002**, *4*, 4677.

(3) For [2 + 2] cycloadditions, see: (a) Kimura, M.; Horino, Y.; Wakamiya, Y.; Okajima, T.; Tamaru, Y. *J. Am. Chem. Soc*. **1997**, *119*, 10869. (b) Morimoto, T.; Horiguchi, T.; Yamada, K.; Tsutsumi, K.; Kurosawa, H.; Kakiuchi, K. *Synthesis* **2004**, 753.

(4) For synthesis of heterocycles, see: (a) Larock, R. C.; Zenner, J. M. *J. Org. Chem*. **1999**, *64*, 7312. (b) Grigg, R.; Sridharan, V.; Xu, L.-H. *Chem. Commun*. **1995**, 1903. (c) Dieter, R. K.; Yu, H. *Org. Lett*. **2001**, *3*, 3855. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed*. **1995**, *34*, 1581. (e) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed*. **2000**, *39*, 2285. (f) Brandasma, L.; Nedolya, N. *Synthesis* **2004**, 735. (g) Regás, D.; Palenzuela, J. A. *Synthesis* **2004**, 757. (h) Ishar, M. P.; Kapur, A.; Raj, T.; Girdhar, N. K.; Kaur, A. *Synthesis* **2004**, 775. (i) Sromek, A. W.; Kel′in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed*. **2004**, *43*, 2280.

(5) For polymer synthesis, see: Takagi, K.; Tomita, I.; Endo, T. *Macromolecules* **1997**, *30*, 7386.

(6) (a) *Allenes in Organic Synthesis*; Coppola, G. M., Schuster, H. F., Eds.; Wiley: New York, 1984. (b) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc*. **1990**, *112*, 8042.

(7) Searles, S.; Li, Y.; Nassim, B.; Robert Lopes, M.-T.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.

(8) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc*. **1996**, *118*, 4492.

(9) (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc*. **2001**, *123*, 2089. (b) Zimmermann, M.; Wibbeling, B.; Hoppe, D. *Synthesis* **2004**, 765.

(10) Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett*. **2003**, *5*, 2145.

(11) (a) Tanaka, K.; Otsubo, K.; Fuji, K. *Synlett* **1995**, 993. (b) Brummond, K. M.; Dingess, E. A.; Kent, J. L. *J. Org. Chem*. **1996**, *61*, 6096.

(12) Delouvrie, B.; Lacote, E.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett*. **1996**, *40*, 3565.

(13) (a) Tsuji, J.; Sugiura, T.; Yuhara, M.; Minami, I. *Chem. Commun*. **1986**, 922. (b) Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis* **1987**, 603.

(14) (a) Badone, D.; Cardamone, R.; Guzzi, U. *Tetrahedron Lett*. **1994**, *35*, 5477. (b) Huang, C.-W.; Shanmugasundaram, M.; Chang, H.-M.; Cheng, C.-H. *Tetrahedron* **2003**, *59*, 3635.

(15) (a) Lee, K.; Seomon, D.; Lee, P. H. *Angew. Chem., Int. Ed*. **2002**, *41*, 3901. (b) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc*. **2003**, *125*, 13042.

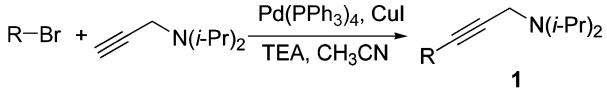
(16) (a) Ma, S.; He, Q. *Angew. Chem., Int. Ed*. **2004**, *43*, 988. (b) Ma, S.; Zhang, A. *J. Org. Chem*. **1998**, *63*, 9601.

(17) Nakamura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc*. **2004**, *126*, 5958.

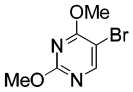
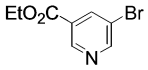
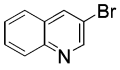
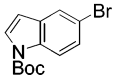
(18) (a) Bleicher, L.; Cosford, N. D. P. *Synlett* **1995**, 1115. (b) Russo, O.; Alami, M.; Brion, J.-D.; Sicsic, S.; Berque-Bestel, I. *Tetrahedron Lett*. **2004**, *45*, 7069.

10.1021/jo0479664 CCC: $30.25
Published on Web 02/04/2005

TABLE 1. Preparation of the Heterocyclic Allene Precursors 1a−h from R-Br by the Sonogashira Coupling Reaction[a]



1

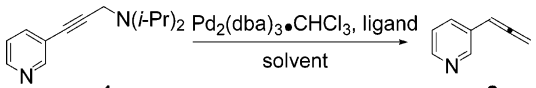
entry	R-Br	propargylic amine, **1**	yield[b] / %
1		**1a**	81
2		**1b**	>99
3		**1c**	95
4		**1d**	79
5		**1e**	>99
6		**1f**	67
7		**1g**	51
8		**1h**	26

[a] All reactions were carried out in the presence of $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %), and Et_3N (150 mol %) in CH_3CN at 60 °C. [b] Isolated yields based on the bromides.

with *N*,*N*-diisopropylprop-2-ynylamine gave the corresponding propargylic diisopropylamine **1h** in 26% yield (entry 8).

The allene transformation reaction of diisopropyl-(3-pyridin-3-yl-prop-2-ynyl)-amine **1a** under various conditions was initially examined (Scheme 3 and Table 2). The reaction progress was monitored by GC analysis. The reaction of **1a** proceeded in the presence of $Pd_2(dba)_3$·$CHCl_3$ catalyst (2.5 mol %) and $(C_6F_5)_3P$ (20 mol %) at 100 °C in dioxane for 48 h, giving 3-pyridylallene **2a** in 96% yield (entry 1). Although the use of THF and ethyl acetate as a solvent gave **2a** in moderate yields (entries 2 and 3), acceleration of the reaction was observed in DMF (entry 4). CH_3CN and $CHCl_3$ were also effective solvents for the reaction (entries 5 and 6). Next, the effect of ligands on the allene transformation was examined. The reactions of **1a** using Ph_3P or $(PhO)_3P$ (20 mol %), as a ligand, at 100 °C in dioxane for 12 h gave **2a** in very poor yields (entries 7 and 8). The use of dppe as a bidentate ligand was effective for the reaction and the yield increased to 57% (entry 9). Interestingly, **2a** was obtained in 94% yield when 1,2-bis[bis(pentafluorophenyl)phosphino]ethane was employed as a ligand (entry 10). Finally, the best result was obtained in the case of entry 11: the reaction of **1a** proceeded in the presence of $Pd_2(dba)_3$·$CHCl_3$ catalyst (2.5 mol %) and 1,2-bis[bis(pentafluorophenyl)phosphino]ethane (10 mol %) at 100 °C in $CHCl_3$ for 24 h, giving **2a**, quantitatively.

TABLE 2. Allene Transformation Reaction of 1a in the Presence Pd_2Dba_3·$CHCl_3$ Catalyst at 100 °C under Various Conditions



1a **2a**

entry	solvent	ligand (mol %)[b]	time, h	yield[a], %
1	dioxane	$(C_6F_5)_3P$ (20)	48	96
2	THF	$(C_6F_5)_3P$ (20)	24	80
3	AcOEt	$(C_6F_5)_3P$ (20)	24	79
4	DMF	$(C_6F_5)_3P$ (20)	8	84
5	CH_3CN	$(C_6F_5)_3P$ (20)	24	93
6	$CHCl_3$	$(C_6F_5)_3P$ (20)	24	91
7	dioxane	Ph_3P (20)	12	7
8	dioxane	$(PhO)_3P$ (20)	12	20
9	dioxane	dppe (10)	24	57
10	dioxane	$(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ (10)	24	94
11	$CHCl_3$	$(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ (10)	24	>99

[a] Yields were determined by GC analysis using hexadecane as an internal standard. [b] Four atom equivalents of phosphines toward the Pd_2dba_3·$CHCl_3$ catalyst (2.5 mol %) was used for the reactions.

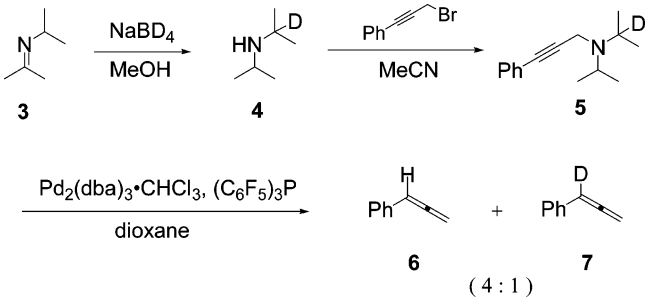
Once a suitable condition for the palladium-catalyzed allene transformation reaction was established, we next investigated the synthesis of various heterocyclic allenes (**2a**−**h**) from the corresponding propargylic amines containing heterocycles (**1a**−**h**) as shown in Table 3. The reaction of **1b**, which was prepared from 5-bromopyri-

TABLE 3. Synthesis of Heterocyclic Allenes from Various Propargylic Diisopropylamines 1a−h via the Palladium-Catalyzed Hydride-Transfer Reaction[a]

entry	propargylic amines **1**	time, h	allene **2**	yield[b] of **2**, %
1	**1a**	24	**2a**	>99[c]
2	**1b**	48	**2b**	89
3	**1c**	28	**2c**	91
4	**1d**	30	**2d**	95
5	**1e**	30	**2e**	86
6	**1f**	24	**2f**	51
7	**1g**	24	**2g**	87
8	**1h**	29	**2h**	88

[a] The reaction was carried out in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst (2.5 mol %) and 1,2-bis[bis(pentafluorophenyl)phosphino]ethane (10 mol %) at 100°C in $CHCl_3$. [b] Isolated yield. [c] GC yield.

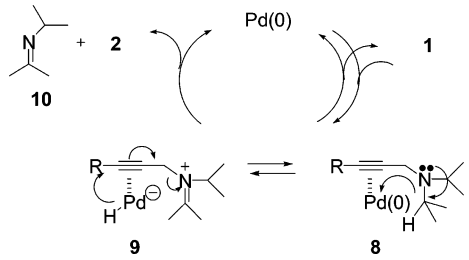
SCHEME 2. Deuterium Labeling Study



midine, was complete after 48 h to give 5-allenylpyrimidine **2b** in 89% yield (entry 2). The dimethoxy pyrimidine **1c**, which can be easily introduced into the uracil derivative by deprotection of methyl ethers, also underwent the allene transformation reaction to afford **2c** in 91% yield (entry 3). An ethyl ester substituted pyridine **1d** was readily transformed into **2d** in 95% yield (entry 4). Although the reaction of **1e** afforded 3-allenylquinoline **2e** in 86% yield (entry 5), the reaction of the isoquinoline **1f** resulted in a lower yield of **2f** (entry 6). The benzo[*b*]-thiophene **1g** and *N*-Boc-protected indole **1h** were also examined, and the corresponding allenes **2g** and **2h** were obtained in 87% and 88% yields, respectively (entries 7 and 8). The transformation reactions of **1b−e** under the combination of $Pd_2(dba)_3{\cdot}CHCl_3/(C_6F_5)_3P$ catalyst at 100 °C gave the corresponding allenes **2b−e** in lower yields (40−68%) compared to previous reports.[17]

To clarify the mechanism of the current allene transformation reaction, a deuterium labeling study was performed as shown in Scheme 2. The reduction of the imine **3** generated in situ from acetone and isopropylamine was carried out using $NaBD_4$ to afford the corresponding to the monodeuterium-labeled diisopropylamine **4**, which was treated with 3-bromo-1-phenyl-1-propyne in the presence of K_2CO_3 in MeCN, giving *N,N*-diisopropyl-3-phenylprop-2-ylamine **5** (d-94%). The allene transformation of **5** proceeded in the presence of $Pd_2(dba)_3{\cdot}CHCl_3/(C_6F_5)_3P$ catalyst at 100 °C in dioxane to afford a 4:1 mixture of phenylallene **6** and 1-deurerio-1-phenylallene **7**. This ratio was due to the isotope effect and the hydride-transfer step from the isopropyl carbon would be considered as a rate-determining step in the allene transformation. Based on the result of the deuterium labeling study, the proposed mechanism is shown in Scheme 3. π-Coordination of Pd(0) with **1** at a carbon−

SCHEME 3. Proposed Mechanism



carbon triple bond would form the complex **8** and the hydride transfer from the isopropyl carbon assisted by a lone pair electron of the nitrogen would generate the palladium anion species **9**. The migration of the hydride on palladium to the alkyne moiety of **9** followed by the rearrangement of the π-bond would give the allene **2** and the imine **10**, and palladium(0) is regenerated. Since 1,2-bis[bis(pentafluorophenyl)phosphino]ethane, as well as $(C_6F_5)_3P$, were effective for the allene transformation reaction of heterocyclic compounds, it is considered that these electron-deficient phosphine ligands would stabilize the anionic palladium intermediate **9** in the equilibrium between **8** and **9** to accelerate the generation of allenes **2** in the catalytic cycle. Furthermore, the bidentate phosphine ligand such as 1,2-bis[bis(pentafluorophenyl)-phosphino]ethane would prevent the other heterocyclic molecules from coordinating to the palladium catalyst in the reaction. Therefore, 1,2-bis[bis(pentafluorophenyl)-phosphino]ethane is more suitable than $(C_6F_5)_3P$ in the current transformation of heterocyclic allenes. It has been reported that the iminium ion can be generated by the insertion of palladium coordinated to the nitrogen lone pair into the carbon−hydrogen bond adjacent to nitrogen.[19]

In conclusion, we developed a novel synthesis of heterocyclic allenes from the corresponding bromides with *N,N*-diisopropylprop-2-ynylamine, as an allenyl anion equivalent, through the Sonogashira coupling reaction followed by the palladium-catalyzed hydride-transfer reaction. The bidentate phosphine ligand, 1,2-bis[bis(pentafluorophenyl)phosphino]ethane, as well as $(C_6F_5)_3P$, were effective for the allene transformation reaction of heterocyclic compounds. It is now possible to conduct heterocyclic allenes not only as a building block for organic synthesis but also as a biofuctional group for medicinal chemistry.[20]

Experimental Section

Representative Procedure for the Synthesis of 1b by the Sonogashira Coupling Reaction. A mixture of 5-bromopyrimidine (318 mg, 2.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol), CuI (38.1 mg, 0.20 mmol), and *N,N*-diisopropylprop-2-ynylamine (334 mg, 2.4 mmol) was dissolved in acetonitrile (10 mL) under Ar, and triethylamine (0.42 mL, 3.0 mmol) was added. The mixture was stirred at 60 °C for 6 h. The reaction progress was monitored by TLC. The solvent was removed under

(19) (a) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348. (b) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7430. (c) Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* **1990**, *55*, 991.

(20) (a) Krause, N.; Hoffmann-Röder, A. In *Modern Allene Chemistry*; Krause, N., Hashmi, S., Eds.; Wiley-VCH: Weinheim, 2004; p 997. (b) Brummond, K. M.; Chen, H. In *Modern Allene Chemistry*; Krause, N., Hashmi, S., Eds.; Wiley-VCH: Weinheim, 2004; p 1041.

reduced pressure, and the residue was purified by silica gel column chromatography with hexane/ethyl acetate (1/1) to give **1b** (429 mg, >99% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.68 (s, 2H), 3.62 (s, 2H), 3.19 (sept, J = 6.4 Hz, 2H), 1.10 (d, J = 6.4 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 156.4, 120.2, 97.1, 76.7, 48.7, 34.9, 20.6. IR (KBr) 2968, 2233, 1539, 1412, 1383, 1325, 1269, 1184, 1119, 1030 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{19}N_3$ (M^+) 217.1579, found 217.1578.

Representative Procedure for the Synthesis of 2c. A mixture of 3-(2,4-dimethoxy-pyrimidine-5-yl)-prop-2-ynyl-*N*,*N*-diisopropylamine **1c** (86.6 mg, 0.312 mmol), $Pd_2(dba)_3$·$CHCl_3$ (8.1 mg, 0.0078 mmol), and 1,2-bia[bis(pentafluorophenyl)phosphino]-ethane (23.7 mg, 0.031 mmol) was dissolved in dry chloroform (2 mL) under Ar. The mixture was stirred at 100 °C for 28 h in a vial tube. The reaction progress was monitored by TLC. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with hexane/ethyl acetate (5/1) to give **2c** (50.6 mg, 0.284 mmol, 91% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 6.17 (t, J = 6.8 Hz, 1H), 5.11 (d, J = 6.8 Hz, 2H), 3.98 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 167.2, 164.2, 156.1, 108.7, 84.0, 78.7, 54.8, 54.0. IR (KBr) 2953, 1944, 1564, 1468, 1383, 1350, 1283, 1190, 1086, 1009 cm^{-1}. HRMS (EI) calcd for $C_9H_{10}N_2O_2$ (M^+) 178.0742, found 178.0740.

Supporting Information Available: Experimental details and characterization data for compounds **1a**−**h** and **2a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0479664